Kinetic and equilibrium studies of the reactions of 4-nitrobenzofurazan and some derivatives with sulfite ions in water. Evidence for the Boulton–Katritzky rearrangement in a σ-adduct †

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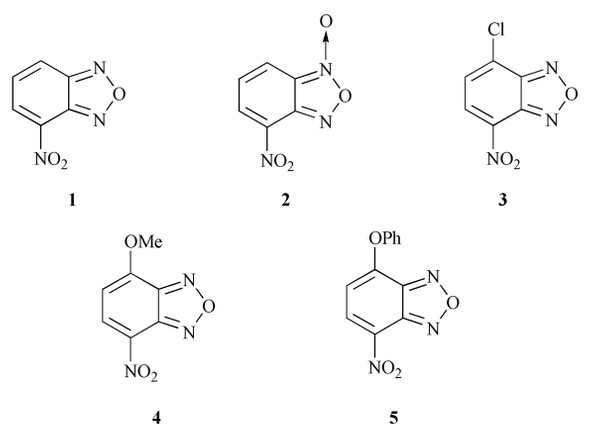
The reactions with sulfite ions in water of 4-nitrobenzofurazan, **1**, 4-nitrobenzofuroxan, **2**, and three 4-nitro-7-substituted benzofurazans have been examined by ^{1}H NMR spectroscopy and stopped-flow spectrophotometry. For each substrate the initial reaction occurs at the 5-position to give σ-adducts which have considerably higher thermodynamic stability than the corresponding adduct of 1,3,5-trinitrobenzene. In the cases of **1** and **2** isomerisation of the 5-adducts occurs slowly to yield adducts carrying sulfite at the 7-position. ^{1}H NMR measurements on **2** labelled with ^{15}N provide evidence that here the rearrangement involves an intramolecular Boulton–Katritzky mechanism.

4-Nitrobenzofurazan, **1**, and 4-nitrobenzofuroxan‡, **2**, are excellent electrophiles and there have been reports of σ-adduct forming reactions with oxygen,[1–5] carbon[5] and nitrogen[6,7] nucleophiles. These studies have generally found a strong kinetic preference for reaction at the 5-position, but with a thermodynamic preference for the adducts formed by attack at the 7-position. However NMR measurements of the reactions of **2** with aryloxide nucleophiles show that here the 7-adducts are both kinetically and thermodynamically favoured.[5] One source of interest in these reactions is the ability of **1** and **2** to act as *in vitro* inhibitors of nucleic acid and protein biosynthesis in animal cells;[8–11] this action is likely to involve σ-adduct formation with cellular sulfur nucleophiles. There is also current interest in the fluorescence characteristics of 4,7-disubstituted benzofurazans.[12–14]

Sulfite readily forms σ-adducts by reaction as a sulfur nucleophile with electron-deficient aromatics.[15,16] Several studies have been reported of adduct formation and nucleophilic substitution resulting from its reaction with trinitro-[17–20] and dinitro-benzene[21] derivatives and also with 4,6-dinitrobenzofuroxan.[22] However there have been no previous studies of its reaction with **1** or **2**. Here we report on such reactions and also, for comparison, reactions with 4-nitro-7-chlorobenzofurazan, **3**, 4-nitro-7-methoxybenzofurazan, **4**, and 4-nitro-7-phenoxybenzofurazan, **5**.

An interesting feature of the results for **1** and the benzofurazan derivatives **3**, **4** and **5** is the high kinetic and thermodynamic stability of the adducts formed by attack at the 5-position. For the benzofuroxan, **2**, there is evidence for an intramolecular, Boulton–Katritzky type, rearrangement of the 5-adduct to the 7-adduct.

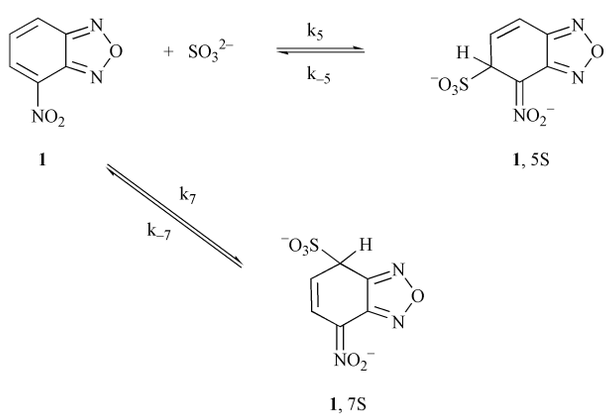


1 **2** **3** **4** **5**

Results and discussion

^{1}H NMR studies

For solubility reasons measurements were made in 80 : 20 (v/v) water–DMSO using deuteriated solvents. Data are summarised in Table 1. The spectrum of **1** in the presence of sulfite indicates initial addition at the 5-position[23] to give **1**, 5S. Very slowly, over a matter of days, conversion occurs to the 7-adduct, **1**, 7S. The spectra of the isomeric adducts can be distinguished principally from the shift of H6 which is expected to have a higher value in 5-adducts than in 7-adducts.[2,3] The results are compatible with the processes shown in Scheme 1. Using the integrated intensities, given in Table 2, of the bands due to the isomeric adducts a value for k_{isom}, the rate constant for isomerisation of $(5.7 \pm 0.5) \times 10^{-6}$ s^{-1} was calculated.



1 **1**, 5S **1**, 7S

Scheme 1

† Electronic supplementary information (ESI) available: Tables S1–S4. See http://www.rsc.org/suppdata/p2/b1/b108591n/
‡ The IUPAC name for furoxan is furazan *N*-oxide.

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Table 1 Spectroscopic data for parent molecules and sulfite adducts

	^{1}H NMR data[a]							
	δ						UV absorbance[b]	
	H5	H6	H7	Other	J_{56}	J_{67}	λ_{max}/nm	ε/dm^3 mol^{-1} cm^{-1}
1	8.72	7.84	8.48	—	7.2	8.8	327	5900
2	8.65	7.57	8.04	—	7.2	9.2	397	6000
3	8.70	7.92	—	—	7.8	—	343	9800
4	8.76	7.01	—	4.24 (OMe)	8.6	—	383	12000
5	8.70	6.72	—	7.45–7.70 (OPh)	8.4	—	380	9500
1, 5S	5.54	6.72	7.04	—	5.8	9.8	327	8500
2, 5S	5.54	6.61	6.69	—	5.4	9.8	327	9800
3, 5S	5.61	6.82	—	—	6.2	—	327	11600
4, 5S	5.52	5.77	—	3.87 (OMe)	6.4	—	328	9100
5, 5S	5.51	5.95	—	7.2–7.5 (OPh)	6.4	—	327	9800
1, 7S	7.13	5.92	5.31	—	10.4	5.0	—	—
2, 7S	7.08	5.82	5.05	—	10.6	4.6	—	—

[a] In 80 : 20 v/v D_2O–[$^2H_6$]DMSO; J values in Hz. [b] In water.

Table 2 Kinetics of isomerisation[a] of **1**, 5S to **1**, 7S

	Relative concentrations[b]		
Time/10^4 s	**1**, 5S	**1**, 7S	k_{isom}[c]/10^{-6} s^{-1}
0	100	0	—
1.08	94	6	5.7
1.86	90	10	5.7
8.73	63	37	5.3
17.5	36	64	5.8
18.2	32	68	6.1
19.2	32	68	5.9
26.0	24	76	5.5

[a] Measurements made at 25 °C in 80 : 20 (v/v) D_2O–[$^2H_6$]DMSO with **1** 0.020 mol dm^{-3} and sodium sulfite 0.018 mol dm^{-3}. [b] From integration of intensities of NMR bands. [c] Calculated as $k_{isom} = (1/t)\ln [a/(a - x)]$ where $(a - x)$ is the relative concentration of **1**, 5S. It is assumed that eventually isomerisation to the 7-adduct is virtually complete.

Table 3 Kinetics of isomerisation[a] of **2**, 5S to **2**, 7S

	Relative concentrations[b]		
Time/10^2 s	**2**, 5S	**2**, 7S	k_{isom}[c]/10^{-4} s^{-1}
0	100	0	—
6.0	73	27	5.2
9.0	56	44	6.4
24	24	76	5.9
28	19	81	5.9
47	10	90	4.9

[a] Measurements made at 25 °C in 80 : 20 (v/v) D_2O–[$^2H_6$]DMSO, with **2**, 0.020 mol dm^{-3} and sodium sulfite 0.018 mol dm^{-3}. [b] From integrated intensities of NMR bands. [c] Calculated as $k_{isom} = (1/t)\ln [a/(a - x)]$ where $(a - x)$ is the relative concentration of **2**, 5S.

The behaviour of 4-nitrobenzofuroxan, **2**, in the presence of sulfite was qualitatively similar to that of **1**. However the data in Table 3 show that the value of k_{isom}, the rate constant for isomerisation, is (5.7 ± 0.5) × 10^{-4} s^{-1} and is *ca.* one hundred times larger than the corresponding value for **1**. In the presence of one equivalent of sulfite the NMR spectra indicated little decomposition of **2**, 7S, the more thermodynamically stable isomer, over a period of two days. However in the presence of excess sulfite irreversible decomposition to unidentified products occurred. The mechanism of isomerisation is considered later.

The NMR spectrum of 4-nitro-7-chlorobenzofurazan in the presence of one equivalent of sulfite, indicates the rapid formation of the 5-adduct, **3**, 5S. There was no detectable change in the spectrum after 24 hours, so that $k_{isom} < 1 \times 10^{-6}$ s^{-1}. Isomerisation would, in this case, produce an adduct, **3**, 7S, which would rapidly expel chloride to yield the product of nucleophilic substitution.[21] There was no evidence for the occurrence of this process. In the presence of excess sulfite, formation of **3**, 5S was followed by irreversible decomposition to give several unidentified products.

Similarly the NMR spectra of **4** and **5** indicate the initial rapid formation of the respective 5-adducts and there was no evidence for displacement of the 7-substituent after 24 hours.

Kinetic studies

Kinetic studies were made in water using stopped-flow spectrophotometry. With each of the compounds **1**–**5** a rapid reaction with sulfite was observed giving rise to an increase in absorbance at 327 nm. In view of the NMR data these changes are interpreted as resulting from sulfite addition at the 5-position of the substrates. Spectroscopic data are given inTable 1. All kinetic measurements were made in solutions with the sulfite concentration in large excess of the substrate concentration, or in buffered solutions where the sulfite concentration was constant. Under these conditions first order kinetics were observed and the rate constant, k_{obs}, is related to sulfite concentration by eqn. (1). The ionic strength was maintained at

$$k_{obs} = k_{-5} + k_5[SO_3^{2-}] \quad (1)$$

I (= 0.5 Σ $c_i z_i^2$) = 0.03 mol dm^{-3} using sodium sulfate as compensating electrolyte.

4-Nitrobenzofurazan, 1. A linear plot according to eqn. (1) with sulfite concentrations 0.001 to 0.01 mol dm^{-3} gave a value for k_5 of (2.8 ± 0.3) × 10^4 dm^3 mol^{-1} s^{-1}. However the intercept was too small to allow the determination of a value for k_{-5}. In order to reduce the concentration of free sulfite ions in solution measurements were made in acidic buffers. Here the concentration of free sulfite ions is related to the stoichiometric concentration by eqn. (2). This uses a value of 7.05 for the pK_a of

$$[SO_3^{2-}]_{Free} = \frac{[SO_3^{2-}]_{Stoich}}{\left(1 + \frac{10^{-pH}}{10^{-7.05}}\right)} \quad (2)$$

the hydrogen sulfite ion in water which is appropriate for the ionic strength of the solutions.[24,25]

The kinetic data in Table 4 give a good fit with eqn. (1) with values of k_5 (3.3 ± 0.3) × 10^4 dm^3 mol^{-1} s^{-1} and k_{-5} 0.02 ± 0.004 s^{-1}. Combination of these values gives K_5 (= k_5/k_{-5})

Table 4 Kinetic and equilibrium data for reaction of **1** with sulfite ions in water at 25 °C and pH 4 [a]

$[SO_3^{2-}]_{Free}/10^{-6}$ mol dm^{-3}	k_{obs}/s^{-1}	k_{calc} [b]/s^{-1}	A [c] (327 nm)	K_5 [d]/10^6 dm^3 mol^{-1}
0	—	—	0.250	—
0.74	0.042	0.044	0.326	2.0
1.70	0.065	0.076	0.342	1.5
2.73	0.102	0.110	0.354	1.7
4.28	0.160	0.16	0.361	1.6
6.00	0.220	0.22	0.367	2.0
7.90	0.30	0.28	0.369	1.9
9.90	0.33	0.35	0.372	—
12.4	0.43	0.43	0.372	—
15.3	0.53	0.52	0.372	—
18.6	0.64	0.63	0.373	—

[a] Acetate buffers. [b] Calculated from eqn. (1) with k_5 3.3 × 10^4 dm^3 mol^{-1} s^{-1} and k_{-5} 0.020 s^{-1}. [c] Absorbance at completion of 5-adduct formation. [d] Calculated as $(A - 0.250)/(0.377 - A)[SO_3^{2-}]_{Free}$.

Table 5 Kinetic data for reaction of **2** with sulfite in buffered solutions at 25 °C in water

Conditions [a]	Range of $[SO_3^{2-}]_{Free}$/mol dm^{-3}	k_5/10^4 dm^3 mol^{-1} s^{-1}
pH = 8	(1–10) × 10^{-3}	6.1
pH = 7	(1–6) × 10^{-3}	6.8
pH = 6	(1–20) × 10^{-4}	7.4
pH = 5	(4–80) × 10^{-6}	6.8
pH = 4	(1–20) × 10^{-6}	6.4

[a] Phosphate buffers at pH 6–8; acetate buffers at pH 4 and 5.

1.65 × 10^6 dm^3 mol^{-1}. This value is in good agreement with that obtained from absorbance data. The similarity of the values obtained for k_5 in the buffered and unbuffered solutions indicates that sulfite rather than hydrogen sulfite is the effective nucleophile.

In order to examine the effects of solvent on the reaction rate measurements were made in unbuffered water–DMSO mixtures. Values of k_5 were found to be 4.4 × 10^4 and 8.8 × 10^4 dm^3 mol^{-1} s^{-1} respectively in 80 : 20 (v/v) and 60 : 40 water–DMSO.

4-Nitrobenzofuroxan, 2. Linear plots according to eqn. (1) of k_{obs} *versus* the concentration of sulfite in buffered solutions gave a value for k_5 (6.7 ± 0.6) × 10^4 dm^3 mol^{-1} s^{-1}. Results in buffered solutions are in Table 5. The independence of k_5 of the pH indicates that, as with reaction of **1**, sulfite is the active nucleophile. Absorbance data in solutions at pH = 4 allowed the calculation of a value for K_5 of (8 ± 2) × 10^6 dm^3 mol^{-1}. This leads to a value for k_{-5} (= k_5/K_5) of (8 ± 2) × 10^{-3} s^{-1}.

4-Nitro-7-chlorobenzofurazan, 3. A plot of k_{obs} *versus* sulfite concentration for unbuffered solutions gave a value for k_5 of (7 ± 1) × 10^4 dm^3 mol^{-1} s^{-1}. The results in solutions buffered at pH 4 are given in Table 6 and lead to values for k_5 of (8.5 ± 1) × 10^4 dm^3 mol^{-1} s^{-1} and k_{-5} 0.02 ± 0.005 s^{-1}. Combination of these values gives K_5 (= k_5/k_{-5}) (4.2 ± 1) × 10^6 dm^3 mol^{-1}, which is in good agreement with the value calculated from absorbance values.

4-Nitro-7-methoxybenzofurazan, 4 and 4-nitro-7-phenoxybenzofurazan, 5. Values for rate and equilibrium constants relating to 5-adduct formation are detailed in Tables S1–S4, given as supplementary information, and are summarised in Table 7.

Comparisons

The results are summarised in Table 7, and are compared with the data for reaction of 1,3,5-trinitrobenzene, TNB, with sulfite in water to give the adduct **6**. The results show the remarkable stability of the sulfite adducts **1**–**3**, 5S with values of K_5 being *ca*. four orders of magnitude higher than the corresponding value for formation of **6**. This difference is noteworthy in view of the rather similar stabilities of the adducts formed by attack of methoxide ions in methanol on **1** and on TNB. Thus for reaction with methoxide, values corresponding to K_5 are 141 dm^3 mol^{-1} for **1** [1] and 23 dm^3 mol^{-1} for TNB.[26] In σ-adduct forming reactions with aliphatic amines in DMSO the equilibrium constants for reaction with **2**, to form adducts **7**, have values between ten and one hundred times *smaller* that those for reaction with TNB to form **8**; the precise ratio depending on the nature of the amine.[6]

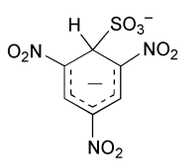

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Table 6 Kinetic and equilibrium data for reaction of **3** with sulfite ions in water at 25 °C and pH 4 [a]

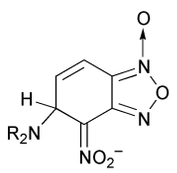
$[SO_3^{2-}]_{Free}/10^{-6}$ mol dm^{-3}	k_{obs}/s^{-1}	k_{calc} [b]/s^{-1}	A [c] (327)	K_5 [d]/10^6 dm^3 mol^{-1}
0	—	—	0.270	—
0.64	0.064	0.074	0.366	4.7
1.6	0.151	0.156	0.379	3.6
2.8	0.253	0.258	0.386	3.5
4.1	0.39	0.37	0.392	5.0
5.9	0.57	0.52	0.395	—
7.5	0.68	0.66	0.395	—
9.6	0.83	0.84	0.395	—
12	1.03	1.04	0.395	—
15	1.33	1.30	0.396	—

[a] Acetate buffers. [b] Calculated from eqn. (1) with k_5 8.5 × 10^4 dm^3 mol^{-1} s^{-1}, and k_{-5} 0.020 s^{-1}. [c] Absorbance at completion of 5-adduct formation at 327 nm. [d] Calculated as $(A - 0.270)/(0.398 - A)[SO_3^{2-}]_{Free}$.

Table 7 Summary of rate and equilibrium data in water at 25 °C

	k_5/dm^3 mol^{-1} s^{-1}	k_{-5}/s^{-1}	K_5/dm^3 mol^{-1}	k_{isom} [b]/s^{-1}	k_7 [b,c]/dm^3 mol^{-1} s^{-1}
1	3.3×10^4	0.020	1.65×10^6	5.7×10^{-6}	(9.4)
2	6.7×10^4	0.008	8×10^6	5.7×10^{-4}	(4600)
3	8.5×10^4	0.020	4.2×10^6	$< 1 \times 10^{-6}$	(< 4.2)
4	8.0×10^3	0.037	2.0×10^5	—	—
5	1.6×10^4	0.016	1.0×10^6	—	—
TNB [a]	3.5×10^4	125	290		

[a] Data from ref. 18 for reaction at unsubstituted ring positions of 1,3,5-trinitrobenzene (TNB). Data have not been statistically corrected. [b] Values in 80 : 20 (v/v) D_2O–[$^2H_6$]DMSO. [c] Calculated as $k_7 = K_5 k_{isom}$.



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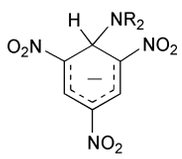

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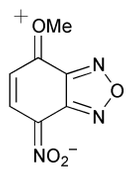

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It is likely that these differences in relative stabilities of the adducts may be partly attributed to the effects of solvation. The data for reaction with sulfite ions were obtained in water, which is known to solvate localised negative charges very effectively.[17,27] Hence the adducts **1**–**5**, 5S, where negative charge is localised on the 4-nitro group, are expected to be well solvated in water. In the adduct **6**, from TNB, the negative charge will be delocalised about the ring and the three nitro groups leading to poorer solvation by water. In contrast DMSO, and, to a lesser extent, alcohols are known[15,16] to solvate anions, such as **8**, carrying delocalised negative charge better than anions, such as **7**, with localised charge; hence the relatively higher stability constants for formation of **8** than of **7**.

It has been argued previously[19] that in σ-adduct forming reactions involving sulfite the transition states are 'reactant like' rather than 'product like'. In agreement with this the data in Table 7 show that changes in the value of the equilibrium constant with substrate structure result mainly from variation in the values of k_{-5}; in particular the value of k_{-5} is *ca.* six thousand times larger for reaction of TNB than for **1**. Also, if transition states are reactant like, the values of k_5 would not be expected to show large variations with the nature of the solvent. The rather small increases in value of k_5 observed for formation of **1**, 5S with increasing proportion of DMSO in the solvent are in accord with this idea; they may reflect some desolvation of sulfite which is virtually insoluble in DMSO.

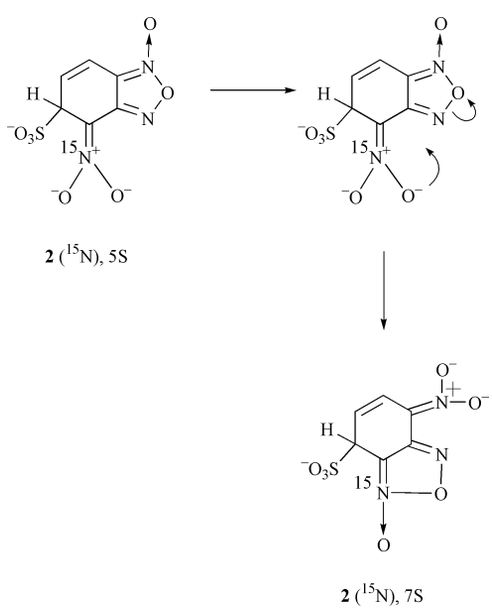
Effects of substituents on stability of the 5-adducts

Comparison of the results for **1** and **2** in Table 7 shows that the introduction of the *N*-oxide function results in a five-fold increase in adduct stability. Here the furoxan moiety is more efficient than the furazan group in adduct stabilisation. A similar difference has been observed in the methoxide adducts.[1]

The σ-*meta* values for Cl, OMe and OPh substituents are reported to be 0.37, 0.08 and 0.25 respectively.[28] Hence the stability of 5-adducts from **3**, **4** and **5** might be expected to be higher than that of the adduct from **1**. This expectation is realised, as shown by the results in Table 7, in the case of the adduct, **3**, 5S, from 4-nitro-7-chlorobenzofurazan. However, the introduction of a methoxy group at the 7-position in **4** results in an eight-fold decrease in adduct stability. This may be attributed to resonance stabilisation of the reactant through cross-conjugation[4,16,29,30] of the methoxy and nitro groups as shown in **9**. Such conjugation will be largely lost in the negativity charged adduct. The small reduction, relative to **1**, in the stability of the adduct from **5** indicates a similar but less pronounced conjugation involving the phenoxy and nitro groups.

The Boulton–Katritzky rearrangement

The data in Table 7 show that the rearrangement of **2**, 5S to **2**, 7S is considerably faster than that of **1**, 5S to **1**, 7S. This is emphasised by the large difference in k_7 values, calculated assuming the dissociative mechanism of Scheme 1. In the case of **1** this is the only feasible mechanism for the re-arrangement. However in the case of **2** an alternative intramolecular pathway for the isomerisation is possible, as shown in Scheme 2, and may be energetically favourable.



2 (^{15}N), 5S

2 (^{15}N), 7S

Scheme 2

The Boulton–Katritzky rearrangement in neutral 4-nitrobenzofuroxan and its derivatives is well documented.[31,32] Likely pathways are opening of the furoxan ring to give a dinitroso intermediate[33] followed by recyclisation, or a one-step process involving a tricyclic, concerted transition state. A computational study of the rearrangement of 4-nitrobenzofuroxan,[34] and a theoretical and experimental study of 5-methyl-4-nitrobenzofuroxan[35] have shown that for these compounds the latter pathway is more likely.

Scheme 2 represents an unprecedented Boulton–Katritzky rearrangement in a negatively charged σ-adduct. In order to test this possibility we made measurements with 4-[^{15}N]nitrobenzofuroxan prepared by nitration of benzofuroxan using [^{15}N]nitric acid. In analogous fashion to previous measure-

Table 8 ^{1}H NMR data[a] for the reaction of 4-[^{15}N]nitrobenzofuroxan, **2** (^{15}N), and sulfite[b]

	δ								
	H5	H6	H7	H7	J_{56}	J_{67}	J_{57}	J_{5N}	J_{6N}	J_{7N}
2 (^{15}N)	8.64	7.57	8.03	7.2	9.0	<1	2.4	<1	<1
2 (^{15}N, 5S)	5.54	6.61	6.69	5.4	9.8	<1	2.0	<1	<1
2 (^{15}N, 7S)	7.08	5.82	5.05	10.5	4.8	1.2	<1	1.2	1.2

[a] Measured in 80 : 20 (v/v) D_2O–[$^2H_3$]acetonitrile, where resolution was improved relative to D_2O–[$^2H_6$] DMSO. *J* values in Hz. [b] Spectra of adducts obtained in solutions containing **2** (^{15}N) 0.020 mol dm^{-3} and sulfite 0.018 mol dm^{-3}.

ments with ^{15}N-labelled 4,6-dinitrobenzofuroxan[36] significant *ortho*-coupling, J_{5N} 2.4 Hz, was observed with the hydrogen at the 5-position. Data are in Table 8, together with values for the 5- and 7-adducts produced in the presence of sulfite. Better resolution was obtained using [$^2H_3$]acetonitrile rather than [$^2H_6$]DMSO as the co-solvent with deuterium oxide. In the initially formed 5-adduct coupling, 2 Hz, is observed between ^{15}N and the adjacent H5. However in the 7-adduct, produced after rearrangement, ^{15}N coupling is with H7, 1.2 Hz, and with H6, 1.2 Hz. This strongly suggests that the 7-adduct is produced, as shown in Scheme 2, by intramolecular rearrangement rather than by the dissociative mechanism of Scheme 1, where coupling of ^{15}N with H5 would be expected. The increased rate of rearrangement of the benzofuroxan derivative is thus attributable to reaction by the Boulton–Katritzky mechanism.

Experimental

4-Nitrobenzofurazan, **1**, was prepared by nitration of benzofurazan using one equivalent of nitric acid in six equivalents of 98% sulfuric acid at 5 °C: mp 92 °C (lit.[9] mp 93 °C). 4-Nitrobenzofuroxan, **2**, was available from previous work:[6] mp 143 °C (lit.[37] mp 143 °C). [^{15}N]-4-Nitrobenzofuroxan was prepared by reaction of benzofuroxan with one equivalent of [^{15}N]nitric acid in six equivalents of sulfuric acid at 5 °C: mp 143 °C. 4-Nitro-7-chlorobenzofurazan, **3**, was a commercial sample. Reaction of **3** with one equivalent of sodium methoxide in methanol for one hour at 40 °C yielded 4-nitro-7-methoxybenzofurazan, **4**: mp 113 °C (lit.[4] mp 115 °C). 4-Nitro-7-phenoxybenzofurazan, **5**, was prepared by reaction at 40 °C for one hour of **3** with one equivalent of sodium hydroxide and ten equivalents of phenol in sufficient water to give a homogeneous solution: mp 117 °C (lit.[38] mp 121 °C). All other materials and solvents were the purest available commercial samples.

^{1}H NMR spectra were measured with Varian Mercury 200 MHz or Varian Unity 300 MHz instruments. UV–vis spectra and kinetic measurements were made at 25 °C with a Perkin-Elmer Lambda 2 spectrophotometer, a Shimadzu UV-2101 PC spectrophotometer or an Applied Photophysics SX-17 MV stopped-flow instrument. Reported rate constants are the means of several determinations and are precise to ±5%. Acetate buffers, *ca*. 0.02 mol dm^{-3}, were used to maintain pH in the range 4–6, and phosphate buffers, *ca*. 0.03 mol dm^{-3}, were used in the pH range 7–8.

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